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MEETING REPORT

Medical Countermeasures against Nuclear Threats: Radionuclide Decorporation Agents

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Exposure to radionuclides disseminated by a radiological dispersion device or deposited as fallout after a nuclear power plant accident or detonation of an improvised nuclear device could result in internal contamination of a significant number of individuals. Internalized radionuclides may cause both acute and chronic radiation injury and increase an individual's risk of developing cancer. This damage and risk can be mitigated by the use of decorporation agents that reduce internal contamination. Unfortunately, most effective agents decorporate only a limited range of radionuclides, and some are formulated in ways that would make administration in mass casualty situations challenging. There is a need for new radionuclide decorporation agents, reformulations of existing agents, and/or expansion of the labeled indications for existing treatments. Researchers developing novel or improved decorporation agents should also understand the regulatory pathway for these products. This workshop, the first in nearly half a century to focus exclusively on radionuclide decorporation, brought together researchers and scientific administrators from academia, government and industry as well as senior regulatory affairs officers and U.S. Food and Drug Administration personnel. Meeting participants reviewed recent progress in the development of decorporation agents and contemplated the future of the field.

INTRODUCTION

Events of the last several years have heightened public concern that terrorists might use weapons of mass destruction (WMDs) against civilian populations. Among WMDs, radiological and nuclear weapons are a particular concern. Such weapons may produce a fission reaction (improvised nuclear device, or IND) or scatter radioactive material (radiological dispersal device, or RDD), surreptitiously or by detonation of conventional explosives. By ingesting or inhaling fallout from an IND or radionuclides dispersed by an RDD, individuals internalize radioactive materials, which can lead to serious health effects. A major goal of therapy in such cases is to administer decorporation agents to enhance elimination of internalized radionuclides through the urine or feces. Because effective decorporation agents have been developed for only a few radionuclides, the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) (*1*) has prioritized development of expanded-spectrum and otherwise novel or improved radionuclide decorporation agents

Within the U.S. Government, the Department of Health and Human Services (HHS) provides leadership in research, development, acquisition, deployment and use of effective radiation countermeasures. The *NIH Strategic Plan and Research Agenda for Medical Countermeasures against Radiological and Nuclear Threats*, published in 2005, outlines the short- and long-term objectives for research and development in this area. The National Institute of Allergy and Infectious Diseases (NIAID) has established a Radiation Countermeasures Program to implement the Strategic Plan and address the Research Agenda. NIAID funds researchers working on promising medical countermeasure candidates, including novel and improved decorporation agents, through cooperative agreements, grants and contracts.

NIAID encourages communication among academic and industry/commercial researchers as well as government agencies involved in medical countermeasure development and drug candidate approval. To this end, on September 17–18, 2007 in Bethesda, MD, the NIAID Radiation Countermeasures Program sponsored a workshop on ''Medical Countermeasures against Nuclear Threats: Radionuclide Decorporation Agents''. Invited speakers (Ta-

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ble 1) and participants discussed the state of the art and future directions for research on radionuclide decorporation agents. This report summarizes the information provided at that meeting. Presentation slides from the workshop can be found at http://www3.niaid.nih.gov/research/topics/radnuc/MeetingSlides.htm.

OVERVIEW AND NEEDS

Dr. Albert Wiley described the threat that radionuclides pose and the basis of treatment for internal contamination, summarizing the recommendations contained in the National Council on Radiation Protection and Measurements (NCRP) Report No. 65 (*2*). Researchers have studied the health effects of internal radionuclide exposure in workers contaminated in industrial accidents as well as in members of the public with internal contamination as a result of contact with unsecured radiation sources.

Ionizing radiation causes damage to DNA, which can lead to cell death, apoptosis, mutations and cancer. The degree of damage sustained depends on the quality of the ionizing radiation producing the injury. High-energy γ and X rays are highly penetrating but produce less dense ionization, whereas α particles have short ranges and produce dense ionization. Because α particles are not highly penetrating, they can cause injury and subsequent health effects only when they are internalized.

Radionuclides may be internalized as a result of inhalation, ingestion, injection or absorption through intact or abraded skin. Once internalized, radionuclides are distributed to various tissues with patterns that depend on the chemical and physical form of the radionuclide in question. In turn, the tissue distribution of a radionuclide determines the pattern of injury observed.

When radionuclides are inhaled, deposition is determined by particle size, with smaller particles traveling further and more efficiently into the pulmonary system to the alveoli, where clearance is slow. Biodistribution of inhaled radionuclides is also heavily influenced by their physicochemical properties. Soluble forms, especially if deposited into the alveoli, are readily taken up into the bloodstream, but insoluble forms, such as oxides, often have a long pulmonary residence time.

Damage from ingestion of radionuclides depends on the degree of gastrointestinal (GI) absorption that occurs and the transit time of unabsorbed material. Absorbed material is distributed systemically and can cause manifestations of acute radiation syndrome at sufficiently high doses, whereas unabsorbed material may cause direct damage to the gastrointestinal mucosa. Alkali metals (e.g. cesium) are almost completely absorbed, while GI absorption of lanthanides and actinides is very low ($<1\%$).

Persons internally contaminated with radionuclides are generally treated with metal chelating agents that bind to the radionuclide and are subsequently eliminated. Because chelating agents have different binding specificities for different metals, the type and level of radionuclide exposure must be assessed to the appropriate chelating agents can be chosen. While whole-body counting can indicate contamination with γ rays and high-energy β-particle emitters, in most cases, the presence of low-energy β- and α-particle emitters will be detected only by assaying biological samples such as urine, feces, sputum and/or nasal swabs.

The U.S. Food and Drug Administration (FDA) has approved Prussian blue capsules (Radiogardase®, Heyl, Berlin, Germany) for internal contamination with cesium and calcium- and zinc-diethylenetriaminepentaacetic acid (Ca- and Zn-DTPA, Hameln Pharmaceuticals, Hameln, Germany), administered intravenously (i.v.) or by nebulizer, for contamination with transuranic radionuclides (e.g. plutonium, americium and curium). Prussian blue, taken orally, is not absorbed by the GI tract, but it binds cesium ions in the gut, thereby enhancing fecal excretion. After the 1987 contamination incident in Goiânia, Brazil, Prussian blue was used successfully, reducing whole-body committed radiation doses by up to a factor of two (*3, 4*). Ca- and Zn-DTPA have been used to treat numerous workers with occupational exposure to plutonium and americium.

Dr. Fred Harper, who has studied the fragmentation and aerosolization properties of a variety of materials in controlled explosions, described the fate of materials used in RDDs (*5*). Such studies have expanded our understanding of the threats that RDDs pose to people in the immediate vicinity of the explosion as well as to first responders and cleanup workers.

Dr. Harper's group has found that for most scenarios, the contaminated zone (defined as a 0.01-Gy/h perimeter) would extend no more than 500 meters from the release. Moreover, respirable particles would remain aloft in the plume for no more than 10 min and thus would pose only a transient hazard for first responders. The identity of the radioactive material and its dispersal pattern might not be known immediately, but first responders can proceed as if a large-scale release has occurred and implement a rapid or phased evacuation (innermost area first—particularly buildings within the impact zone) to a safe triage area where decontamination, assessment and treatment can begin.

Dr. Joanna Prasher described the key role that the Biomedical Advanced Research & Development Authority (BARDA) plays in the development of medical countermeasures against WMDs and other public emergencies. A new agency within the U.S. Department of Health and Human Services, BARDA works with other HHS agencies to oversee advanced product development and procurement of medical countermeasures for chemical, biological, radiological and nuclear agents as well as medical countermeasures for emerging infectious diseases and pandemics, including pandemic influenza. The decorporation agents Ca- and Zn-DTPA and a pediatric formulation of the thyroid blocking agent potassium iodide have already been procured for the Strategic National Stockpile (SNS), using the fund authorized by the Project BioShield Act of 2004. The SNS has

TABLE 1
Invited Workshop Speakers

Name	Affiliation	Title
H. Vasken Aposhian, Ph.D.	University of Arizona	Polonium-210 and Sulfhydryl Chelating Agents
Raymond J. Bergeron, Ph.D.	University of Florida	Desferrithiocin Analogue Actinide Decorporation Agents
Raymond A. Guilmette, Ph.D.	Los Alamos National Laboratory (now at Lovelace Biomedical and Environmental Research Institute)	Radionuclide Chelation Animal Experiments and Animal Models, Biokinetics of Radionuclides and Calculation of Whole-Body/Tissue Committed Dose
Frederick T. Harper, Ph.D.	Sandia National Laboratory	Radiological Dispersal Devices: Physically Based Dispersal Characteristics and Limitations
Michael Jay, Ph.D.	University of Kentucky	Development of Improved DTPA for Radionuclide Chelation: Prodrug Approach
Barry L. Levinson, Ph.D.	Aton Pharma, Inc.	Use of Sypine® and Cuprimine®, FDA-Approved Therapeutics for Wilson's Disease, as Oral Radioisotope Decorporation Agents
Tatiana G. Levitskaia, Ph.D.	Pacific Northwest National Laboratory	Biomaterials as Decorporation Agents for Radionuclides
Scott D. Miller, Ph.D.	University of Utah	Amphipathic Oral Chelators and Radionuclide Contamination
Narayan Nair, M.D.	Office of Counter-Terrorism and Emergency Coordination, Food and Drug Administration	Licensure of Radionuclide Chelating Agents
Joanna M. Prasher., Ph.D.	Biomedical Advanced Research & Development Authority, Department of Health and Human Services	Development and Acquisition of High Priority Radionuclide Medical Countermeasures —HHS/BARDA Roles and Responsibilities
Kenneth N. Raymond, Ph.D.	University of California Berkley/Lawrence Berkeley National Laboratory	Biomimetic Lanthanide & Actinide Decorporation Agents: Preclinical Development
Gita N. Shankar, Ph.D.	SRI International	Development of Improved DTPA for Radionuclide Chelation: Transport Enhancers
Charles Timchalk, Ph.D.	Pacific Northwest National Laboratory	Development of Selective Nanoporous Sorbents for Radionuclide Decorporation
Albert L. Wiley, M.D., Ph.D.	Radiation Emergency Assistance Center/Training Site (REAC/TS), Oak Ridge Institute for Science and Education	Health Effects of Radionuclides and Current Treatments

also directly acquired an additional decorporation agent, Prussian blue. These acquisitions have enhanced U.S. preparedness for many radionuclide threats, but improved or expanded-spectrum chelators are still needed to provide protection against other radionuclides for which no licensed decorporation agents currently exist and to allow improved efficiency of use during an emergency. BARDA manages the HHS medical countermeasure strategic planning process, which entails threat identification and prioritization, estimation of the medical and public health effects of plausible high-consequence scenarios, establishment and prioritization of medical countermeasure requirements, and development of near-, mid- and long-term development, acquisition and delivery strategies. As summarized in the *HHS Public Health Emergency Medical Countermeasures Enterprise Implementation Plan for Chemical, Biological, Radiological and Nuclear Threats (April 2007)* (*1*), HHS is forecasting acquisition of radionuclide-specific agents in the mid-term (FY09–FY13).

PATHWAY TO LICENSURE OF COUNTERMEASURES

Dr. Narayan Nair, representing the FDA Office of Terrorism Prevention and Emergency Response, described regulatory pathways that exist for medical countermeasures, with a particular focus on decorporation agents. Generally, products procured for the SNS must either be FDA-approved or have sufficient data on safety and efficacy filed at FDA to be administered under an Investigational New Drug protocol or an Emergency Use Authorization. Designing clinical trials to evaluate the efficacy of novel radionuclide decorporation agents in humans is not feasible, however, since accidental internal contamination is a rare event and since it would not be ethical to expose human subjects to radionuclides solely for the purpose of testing an agent.

Because such difficulties are inherent to the development of medical countermeasures against WMD threats, the FDA has established the Animal Efficacy Rule (21 CFR 314 Subpart I and 21 CFR 601 Subpart H). Under the ''Animal Rule'', pivotal efficacy testing can be performed in animals when

1. the mechanisms of injury and radionuclide elimination as a result of the treatment are reasonably well understood,
2. efficacy is demonstrated under Good Laboratory Practice (GLP) conditions in more than one animal species (unless one species has a very well-understood response that is known to be characteristic for humans),
3. the study end point is related to the benefit in humans, and

4. an effective human dose can be determined by human and animal pharmacokinetic and pharmacodynamic studies.

The data package supporting a medical countermeasure indication must include human safety studies. Additionally, candidate medical countermeasures must be produced in compliance with current Good Manufacturing Procedures (cGMP). The sponsor of a candidate medical countermeasure must provide the FDA with a post-marketing plan to evaluate safety and efficacy in humans actually treated for the licensed indication when such studies are feasible and ethical.

Guidelines for the testing of decorporation agents have been published by the FDA (http://www.fda.gov/cder/guidance/6983fnl.htm) (*6*). According to the guidelines, a demonstration of efficacy can be based on ''direct measurement of the elimination of the radioactive contaminant through feces and/or urine (or exhalation as appropriate) at various time points after administration of the decorporation agent; alternatively, the residual body burden may be measured.'' Such measurements can then be used to support drug approval by demonstrating that the candidate countermeasure confers a ''clinically-meaningful reduction in whole-body committed radiation dose.'' Because data on product use in humans may be limited to safety studies, the number of subjects required may be increased relative to normal Phase I clinical safety studies for a candidate drug using the traditional approval pathway. According to the guidelines, ''for products that (1) are intended to treat conditions for which there are no available therapies, (2) meet an unmet medical need, (3) are intended for short-term use, or (4) have a well-defined and acceptable toxicity profile in animals, 200 to 300 subjects may be sufficient to support approval, if those subjects have been exposed to the decorporation agent at doses and durations comparable to those anticipated in marketed use and have had an adequate battery of safety testing.'' The requirements for each decorporation agent would be determined on a case-by-case basis, so it is imperative that a drug's sponsor contact the appropriate FDA Division as well as the FDA Office of Counter-Terrorism and Emergency Coordination early and work closely with them throughout the development process.

Dr. Ray Guilmette presented a historical overview of research on decorporation agents that included a lengthy discussion of animal models, citing Durbin *et al.* (*7*) as an example. In Dr. Durbin's studies, candidate chelating agents were administered to mice approximately 1 h after injection with radionuclide. Radionuclide levels in urine and feces and residual radionuclide burden in selected tissues were then determined to allow for comparison among different candidates. The optimal dose and schedule, including longer timings between exposure and initial administration of agent, still need to be studied for each lead candidate.

Dr. Guilmette argued that studies of decorporation agents should also include realistic contamination scenarios, such as inhalation (*8*). If radionuclides are inhaled, the lungs become a target organ for toxicity, necessitating a treatment regimen that enhances lung clearance. Guilmette and Muggenburg found that i.v. administration of Ca-DTPA reduced lung, liver, bone and kidney deposition of inhaled $^{241}AmO_2$ in dogs, with continuous infusion being particularly effective. Muggenburg *et al.* (*9*) also found that lung lavage of dogs that inhaled ^{144}C-infused aluminosilicate particles resulted in decreased radionuclide levels and increased mean survival time. Furthermore, several studies (*9–12*) showed that dose reduction as a result of therapy reduced tumor incidence and increased survival time. Although these treatments may not be suitable for a mass casualty situation, these experiments provide a benchmark by which treatments may be judged, and they can guide researchers in selecting relevant methods and end points.

U.S. FDA-LICENSED CHELATORS: POTENTIAL FOR LABEL EXTENSION FOR RADIONUCLIDES OF INTEREST

British Anti-Lewisite (BAL) and its Derivatives for Polonium Decorporation

The poisoning death of Alexander Litvinenko with ^{210}Po has drawn attention to the unique properties of this radionuclide and has prompted concern about its potential use by terrorists. Enhancing elimination of ^{210}Po could decrease toxicity and lethality caused by internal contamination; therefore, researchers have evaluated a number of chelators to determine their effectiveness as decorporation agents for this radionuclide. Dr. H. Vasken Aposhian discussed the sulfhydryl-containing agent dimercaprol (British anti-Lewisite, BAL, 2,3-dimercaptopropanol) and its derivatives: meso-2,3-dimercaptosuccinic acid (DMSA), 2,3-dimercapto-1-propanesulfonic acid (DMPS), and dimercaptopropylphthalamidic acid (DMPA). Few if any of these products have been tested in humans, although DMPA, monoester analogs of DMSA, and dithiocarbamate chelating agents have shown efficacy as ^{210}Po decorporating agents in rats.

BAL (dimercaprol, BAL-in-Oil™, Akorn Pharmaceuticals, Inc.) received FDA approval in 1946 for decorporation of mercury, arsenic and gold. It is also effective for acute lead intoxication when used with ethylenediaminetetraacetic acid (EDTA) (*13*). Although BAL increases urinary and fecal excretion of ^{210}Po (*14*) and the mean survival time of rats injected with ^{219}Po (*15, 16*), in more recent studies BAL has shown a redistribution of ^{210}Po to the brain (*17*). Since BAL is not bioavailable orally and appears to mobilize ^{210}Po to the brain, derivatives have been developed. DMPS and DMSA, which have the advantage of being both bioavailable orally and less toxic, are both currently approved for use in humans. DMPS (Dimaval®, Heyl, Berlin, Germany), originally licensed in the former Soviet Union in 1958, has been available in the West since 1978 for use

in patients with mercury, arsenic and lead intoxication (*13*); however, it is not currently FDA-approved. In rats, DMPS administration after a lethal subcutaneous injection of ^{210}Po increased survival (*18*) and ^{210}Po excretion and decreased ^{210}Po tissue burden (with the exception of kidneys) (*18, 47*).

DMSA (Succimer, Chemet®, Ovation Pharmaceuticals, Inc.) received orphan drug designation from the FDA for the treatment of lead poisoning in children (1984), prevention of cystine kidney stone formation in those homozygous for cystinuria (1990), and mercury intoxication (1991). As with DMPS, DMSA is available orally in a capsule formulation, is less toxic than BAL, and does not mobilize metals to the brain (*19*). The efficacy of DMSA for ^{210}Po decorporation has been evaluated in rats. The drug appears to provide only a modest benefit. Compared to controls, DMSA treatment did not decrease total-body ^{210}Po but increased ^{210}Po levels in the kidneys (*17, 20*). In other experiments, total excretion of ^{210}Po after DMSA treatment was 12% compared to 7% in untreated animals, and ^{210}Po was redistributed to the liver and kidney (*21*). DMSA given by subcutaneous or gastric lavage 1 h after lethal ^{210}Po exposure increased survival compared to controls, but when DMSA administration was delayed until 3 or 24 h after ^{210}Po injection, the mean survival time did not differ significantly from controls (*18*).

Penicillamine and Trientine

Dr. Barry Levinson discussed the potential for developing a label extension for penicillamine (Cuprimine®, Aton Pharma, Inc.) and trientine (Syprine®, Aton Pharma, Inc.) for ^{60}Co and/or ^{210}Po decorporation.

The thiol penicillamine is FDA-approved for the treatment of Wilson's Disease (an autosomal recessive genetic disorder of copper metabolism), rheumatoid arthritis and cystinuria (*22*). This compound is also listed on the Radiation Event Medical Management website (http://www.remm.nlm.gov) as a countermeasure for decorporation of copper, iron, mercury, lead, gold and possibly other heavy metals (NIST Standard Reference Database 46, 1997) (*23, 24*). Le demonstrated that penicillamine (given orally or i.v.) was a more effective decorporation agent than EDTA and DTPA in rats internally contaminated with ^{60}Co (*25*). The data for humans are limited, but in a small (two patients) study, penicillamine treatment did increase urinary excretion of ^{60}Co (*26*).

The polyamine trientine (triethylenetetraamine) is also FDA-approved for the treatment of Wilson's Disease, specifically for those individuals who are penicillamine intolerant, and is now regarded by many as the preferred first-line management for this disorder (*27*). Trientine forms a stable complex with the metal through interactions with its four nitrogens and demonstrates strong binding to copper, mercury, nickel, bismuth and palladium, and to a lesser extent zinc, cadmium, lead and cobalt (NIST Standard Reference Database 46, 1997) (*23*). To our knowledge, no *in vivo* experiments have been conducted in animals or humans to assess the efficacy of trientine as a decorporating agent for metals that would likely be encountered in a radiological or nuclear event.

NIAID-SPONSORED RESEARCH AND DEVELOPMENT OF MEDICAL COUNTERMEASURES FOR RADIONUCLIDE DECORPORATION: IMPROVEMENT OF DTPA FORMULATION

Although Ca-DTPA and Zn-DTPA are approved for decorporation of internal transuranic radionuclides, the requirement for i.v. injection or administration by nebulization limits their utility in a mass casualty situation. Thus an improved DTPA formulation that is more suitable for a mass casualty situation (e.g. oral administration) would be desirable. In 2005, the NIAID awarded contracts for ''Development of Improved DTPA for Radionuclide Chelation'' to the University of Kentucky (Lexington, KY), SRI International (Menlo Park, CA), and Nanotherapeutics Incorporated (Alachua, FL). Dr. Michael Jay (University of Kentucky) and Dr. Gita Shankar (SRI International) presented their research findings.

Dr. Jay and colleagues use pro-drugs to promote enhanced uptake of orally administered DTPA and increased plasma DTPA levels. Pro-drugs are made by esterifying the carboxylic acid groups of DTPA to lipophilic moietites. They hypothesize that the pro-drug is taken up by the gut and converted back to DTPA after absorption. Preliminary studies of their lead candidate formulation demonstrate significant oral bioavailability, favorable pharmacokinetics, and conversion of the pro-drug to the active compound, with effective radionuclide decorporation in rodents. Dr. Jay continues to refine and develop the pro-drug formulation to improve decorporation efficacy. He also plans to optimize the drug dose and administration schedule and develop cGMP manufacturing of a formulation suitable for GLP animal and human safety studies.

Dr. Shankar is developing an orally bioavailable formulation of DTPA using absorption enhancers. Various formulations were evaluated *in vitro* to determine mucosal-to-serosal and serosal-to-mucosal transport across rat intestinal segments, and selected formulations were then examined *in vivo* for oral bioavailability. SRI's DTPA formulation increased bioavailability to ~30% in rats and 38% in canines compared to only 5% bioavailability with oral administration of the currently licensed parenteral product. In a proof-of-concept study performed in collaboration with Dr. Kenneth Turteltaub at Lawrence Livermore National Laboratory, Ca-DTPA and Zn-DTPA formulated in minicapsules (with SRI absorption enhancers) were administered orally to rats daily, starting 1 h after i.v. administration of the radionuclide ^{241}Am. Effective elimination of the ^{241}Am was obtained with the orally formulated product. Approximately 34–42% of the total ^{241}Am was eliminated within the first 96 h, as measured from the collected urine and feces,

through once-daily administration of the SRI-formulated DTPA minicapsules In comparison, about 82% of the total ^{241}Am dose was excreted in the first 96 h when the rats were administered an equivalent once-daily amount of DTPA i.v. Dr. Shankar is continuing development, and studies are under way to refine the formulation scale-up, optimize the dose and schedule, improve radionuclide elimination, and perform U.S. FDA Good Laboratory Practice (GLP) animal safety studies.

NIAID-SPONSORED RESEARCH AND DEVELOPMENT OF MEDICAL COUNTERMEASURES FOR RADIONUCLIDE DECORPORATION: NOVEL CHELATORS

Siderophore Analogs for Actinide Decorporation

Due to the limitations of DTPA for decorporating uranium and transuranic metals (*28*), researchers have explored other agents for this purpose. For example, siderophores and iron binding agents have been researched, since Fe(III) and the actinides [e.g., Pu(IV) and Am(III)] have similar distribution, charge-to-radius ratio, and biological transport (*29*). Hence siderophores, some of which have been tested in humans for iron decorporation, have served as the backbone for rational modifications to create analogues for decorporation of uranium and other transuranics (*30*).

Dr. Raymond Bergeron (University of Florida) discussed desferrithiocin and its derivatives. This agent, although an orally effective iron chelator, has unacceptable renal toxicity. Hence his group began searching for less toxic analogues for uranium decorporation. This search resulted in the identification of several orally available analogues with improved decorporation and toxicity profiles. In rats, reduced toxicity from the analogues led to a significant increase in fecal excretion of the chelated compound. This resulted in a net reduction of uranium within the body, especially the kidneys. In contrast, DTPA was ineffective at decorporating uranium.

Dr. Kenneth Raymond (University of California, Berkeley) then presented a review of published data on hydroxypyridone analogues. This overview included their use in preclinical models as a decorporating agent for plutonium, americium, thorium and uranium as well as data from toxicity and efficacy studies. Dr. Raymond's group has identified two lead hydroxypyridinonate compounds, octadentate 3,4,3-LI-1,2-HOPO and tetradentate 5-LIO-Me-3,2-HOPO, as effective and safe decorporating agents for actinides in rodents. For example, 3,4,3-LI-1,2-HOPO, which can be given orally, is a more potent actinide decorporating agent than $CaNa_3$ DTPA while demonstrating no overt toxicity (*31*). In a later study, Volf and colleagues demonstrated that this agent was still able to decorporate plutonium and americium when given 5 days after exposure, but to a lesser extent (*32*). Comparative toxicity studies of 3,4,3-LI-HOPO and DTPA in baboons demonstrated no apparent toxicity (*33*).

Amphipathic Oral Chelators

Dr. Scott Miller (University of Utah) discussed his research on amphipathic polyaminocarboxylic acid chelators, which are based on triethylenetetramine-hexaacetic acid (TT) and are structurally similar to DTPA. The TT compounds are available orally and, if necessary, could be altered for preferential uptake into specific tissues and excretion through the biliary (more lipophilic) or urinary (more hydrophobic) system. Hence the more lipophilic agents are more efficient at removing metals that have accumulated in the liver, and they may also reduce renal toxicity. These compounds have one more binding moiety compared to DTPA and appear to have a broader range of binding affinities for heavy metals, including thorium, samarium, plutonium, americium, uranium, strontium, cobalt and others (*34–36*). Decorporation by TT was directly correlated with lipophilicity; however, orally administered compounds did not perform as well as Zn-DTPA administered parenterally. For example, when administered to rats in food, C_{22}TT, the best TT chelator for which published data are available, did not decorporate americium as effectively as subcutaneous Zn-DTPA (*36*). Other preliminary data in rats demonstrate the potential for TT to decorporate uranium and cobalt effectively.

Biomaterials: Chitosan

Dr. Tatiana Levitskaia of the Pacific Northwest National Laboratory discussed chitosan, the main derivative of chitin, as a potential decorporating agent for strontium, radium, cobalt, americium, plutonium, uranium and potentially other radionuclides. Chitin and its derivatives (e.g. chitosan) are non-toxic, and chitin is an abundant and renewable natural biopolymer, second only to cellulose in abundance. Furthermore, chitosan can readily be modified chemically to make it more suitable as a decorporating agent for other metals such as cesium.

Nishimura and colleagues have reported that whole-body retention of ^{85}Sr in rats was significantly lowered by oral administration of chitosan (*37*). The authors suggest that in the GI tract, strontium phosphate forms an insoluble complex with the chitosan, which is then eliminated. Carbon-14-labeled chitosan is digested in the GI tract of mice and distributed throughout tissue (*38*). Nishimura and colleagues also showed that chitosan improves hematopoiesis, possibly through free radical scavenging of chitosan (or derivatives) (*39*). This translates into a 20% survival benefit in mice after whole-body irradiation.

Nano-engineered Sorbents

Dr. Charles Timchalk of the Pacific Northwest Laboratory discussed a new class of nanostructured sorbents: self-assembled monolayer on mesoporous supports (SAMMS) materials, which were developed to facilitate radioactive complex waste cleanup at Department of Energy sites. SAMMS are hybrid materials of mesoporous silica (SiO_2) that are covalently linked to selective organic moieties.

Chosen based on the desired chelating properties, SAMMS chelation is enhanced by high surface area of the silica substrate (~1,000 m^2/g), high functional group density, and a pore size that enhances rapid, effective chelation of the ion (*40, 41*). SAMMS have been shown to effectively chelate uranium, plutonium, americium, iodine, cobalt, cesium, neptunium, thorium and other metals (*40, 42–45*). Dr. Timchalk proposed SAMMS for GI chelation of radionuclides by insolubilizing the metal to prevent systemic absorption, thereby enhancing excretion through this route. He also discussed the potential use of SAMMS for extracorporeal blood chelation by circulating blood through an external microfiltration device containing SAMMS.

DISCUSSION

If a radiological dispersal device were to explode, the response would include the physicochemical identification of the radionuclide and the medical management of trauma and external and internal radionuclide contamination (*46*). Although external decontamination can be accomplished by simple actions such as removal of contaminated clothing and washing, the tendency for radionuclides that are taken internally to be distributed to organs and the harm that these radionuclides can cause pose a challenge for the medical practitioner. The challenges are compounded when a large number of people are affected, and treatments must be suitable for mass casualty situations. The primary type of treatment available for internal radionuclide contamination is the use of decorporation agents, and the meeting discussed here focused on the context, history and use of current and future decorporating agents.

Radionuclide contamination has been a concern of the nuclear industry, and treatments have been developed for workers who are accidentally exposed to radionuclides. With the possibility of a terrorist incident involving radionuclides, these treatments must be adapted to a larger population that could be exposed to a variety of agents with a potentially higher number of casualties. The need to protect the general population from the consequences of a large-scale exposure to radionuclides has spurred greater interest from the U.S. government and has led to funding for radiological medical countermeasure research, starting with treatments that have already been approved. The goals of the NIAID Radiation Countermeasures Program are to develop radionuclide decorporation agents that

1. chelate and eliminate a range of radionuclides,
2. are effective for radionuclide contamination by different routes (inhalation, ingestion and transdermal),
3. are administered orally,
4. are effective when administration is delayed long after radionuclide exposure, and
5. are safe for all potential populations including infants, children and the elderly.

The only drugs approved for radionuclide decorporation are Prussian blue for cesium and thallium decorporation and Ca- and Zn-DTPA for americium, curium and plutonium decorporation. These treatments are limited by the kinds and types of radionuclides for which they are effective. In addition, DTPA is administered i.v. and therefore is not optimum for a mass casualty situation. Further research is needed to improve DTPA formulations and to develop novel radionuclide chelating agents. Funding provided by the NIAID has stimulated the development of several promising new radionuclide decorporation agents. This meeting provided a snapshot of the research that was begun under these initiatives, the potential for further candidates, and the challenges that researchers face in getting these candidates through the development process. Promising results have been shown for oral forms of DTPA, which show increased bioavailability while maintaining the ability to decorporate radionuclides. In addition, further research into drugs that have been in development for some time (such as desferrithiocin derivatives, the HOPO compounds and the triethylenetetramine-hexaacetic acid derivatives) has been stimulated by new funding. In addition, novel approaches using chitosan analogs and nanostructured sorbents for extracorporeal treatment have been identified.

The identification of promising candidates and proof-of-principle testing is one challenge faced by the NIAID Radiation Countermeasures Program and researchers in the field; another challenge is the requirements for the pathway to licensure. Testing of candidate agents in people is not ethical or feasible, but the FDA's ''Animal Rule'' provides a mechanism for approval of medical countermeasures for nuclear events. In general, the demonstration of decorporation efficacy would be necessary for approval, but specific approval pathways for a new radionuclide decorporation agent will be determined on a case-by-case basis since each agent would have different chelating properties, and a wide range of exposure scenarios would be possible. However, there are substantial historical data and information collected over several decades documenting the disposition, biokinetics and decorporation of a wide range of radionuclides in various animal models and with various routes of contamination. These data will be useful in determining and planning the studies that will be required for FDA licensure. To continue the development and licensure of new decorporation agents, specialized facilities capable of performing efficacy studies in compliance with GLP (21CFR58) will be needed. As with much of the radiation research infrastructure, these facilities have not been maintained since the end of the Cold War, and upgrades need to be made, a process that has been started by NIAID.

The NIAID-sponsored Decorporation Workshop provided an important bridge between the past research into radionuclide decorporation and the current and future research, with an eventual goal of increasing the options for practitioners treating patients with internal radionuclide contamination through accidental or deliberate exposure.

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